UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,012	02/20/2004	Pramod K. Srivastava	8449-298-999	2496

20583 7590 08/07/2006

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/784,012	SRIVASTAVA, PRAMOD K.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *4-14, 16, 18, 21, 22, 24, 34 and 36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,15,17,19,20,23,25-33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: Srivastava

1. Applicant's election of Group II (claims 1-3, 7-10, 15, 17, 19, 20, 23, 25-33 and 35) and species election of chemotherapeutic agent in the reply filed on 6/6/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-39 are pending. Claims 4-14, 16, 18, 21, 22, 24, 34 and 36-39 are withdrawn from further consideration as being drawn to non-elected inventions.

3. Claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are under examination.

4. Due to species election, claims are examined to the extent wherein the at least treatment modality comprises a chemotherapeutic agent.

Claim Objections

5. Claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are objected to because the claims contain non-elected inventions i.e. heat shock protein. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are indefinite for reciting the phrase "at least 50% of the different proteins presented in cells" in claims 1-3. The meaning of this phrase is unclear. Does is mean that the number of the proteins is 50% of that of the total proteins presented in a cell? What is the number of the total different proteins presented in a cell?

B. Claim 19 recites the limitation "wherein the cells of same type of cancer" in 1, 2 or 3. There is insufficient antecedent basis for this limitation in the claim. Claims 1, 2 or 3 only recites "the cells of said type of cancer".

Claim Rejections - 35 USC § 112, 1st paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a type of cancer comprising administering to a subject in need of such treatment a composition comprising a population of complexes, said complexes comprising alpha-2-macroglobulin and antigenic proteins, does not reasonably provide enablement for a

method of preventing a type of cancer comprising administering to a subject in need of such prevention a composition comprising a population of complexes, said complexes comprising alpha-2-macroglobulin and antigenic proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection is made because applicants claim a method for preventing a cancer.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claims are drawn to a method of treating or preventing a type of cancer comprising administering to a subject in need of such treatment or prevention a composition comprising a population of complexes, said complexes comprising alpha-2-macroglobulin and antigenic proteins, and administering to said subject at least one treatment modality that does not comprise a alpha-2-macroglobulin.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v.

Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

Claims are drawn to a method of treating or preventing any type of cancer.

The unpredictability of the art and the state of the prior art

No material has been found to date that has been shown to or would be expected to prevent cancer, and there is no working example, prior art, or any evidence that would provide the skilled artisan with any predictable guidance to use the claimed invention, it would be reasonable to conclude the claimed invention is not enabled.

Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and link those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

The art teaches that complex of heat shock protein (HSP)/antigenic peptides and alpha-2-macroglobulin/antigenic peptides are effective in treatment of cancer in mice through generation of immunogenic response to the HSP or alpha-2-macroglobulin, and their associated antigenic peptides (see for example, US Patent No. 6,168,793, and US Patent No. 6,984,389). However, nowhere in the art does it show that complex of HSPs/antigenic peptides and alpha-2-macroglobulin/antigenic peptides are effective in preventing cancer. Furthermore, it has been shown that compounds or components that are used for the treatment of cancer are only effective for their therapeutic effect against cancer, and not as part of a prophylactic regimen. One such example found in the art, Evans *et al* (Q. J. Med 1999: 92: 299-307) teach that vaccines against cancer are not fully established, and it is stated that adjuvant therapy to prevent or delay disease still needs experimentation. Evans *et al* further state that such cancer vaccines are at best used as a therapeutic and not as a prophylactic and that *"the notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs to the realm of fiction"* (see page 303 last paragraph).

Heretofore the art has only recognized the treatment of a cancer

Working examples

The specification teach that no tumor growth was observed at day 20 in the mice that were immunized with alpha-2-marcoglobulin or gp96 complex with MethA10 (see specification, page 98). While these results may indicate that the complexes of alpha-2-macroglobulin or gp96 could delay the growth of a specific tumor in mice, these data are

not sufficient to indicate to one skilled in the art that these immunogenic complexes, when administered to human, are in fact capable of preventing any and all cancers. As stated above, reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and link those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent.

Guidance in the specification

The specification provides insufficient objective evidence to indicate to one of skill in the art that the administration of the alpha-2-macroglobulin complexes would be enabling to prevent cancer.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since prevention of cancer is unpredictable and has not been recognized in the art. The identification, characterization, and validation of a cancer vaccine would be inventive, unpredictable, and difficult in itself, requiring years of inventive effort with no guarantee of success in

doing so.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which provides insufficient evidence to show that cancer prevention is enabling and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Li (US Patent No. 6,984,389, Data of Patent 1/10/2006, earliest effective filing date at least 12/16/2002).

Due to the indefinite nature of the claims (see paragraph 7 above), claim 1 is interpreted as a method of treating a type of cancer, comprising administering to a subject in need of such treatment a composition comprising a population of complexes, said complexes comprising (a) alpha-2-macroglobulin, and (b) antigenic proteins, wherein said population of complexes were produced by complexing alpha-2-macroglobulin to at least 50 different proteins present in the cells of said type of cancer; and administering to said subject at least one treatment modality that does not comprise a alpha-2-macroglobulin, wherein the at least one treatment modality comprises a chemotherapeutic agent.

Claim 2 is interpreted as a method of treating a type of cancer, comprising administering to a subject in need of such treatment a composition comprising a population of complexes, said complexes comprising (a) alpha-2-macroglobulin, and (b) antigenic proteins, wherein said population of complexes were produced by a method comprising digesting a protein preparation comprising at least 50 different proteins present in cells of said type of cancer with one or ore proteases to produce a population of antigenic peptides, and complexing the populations of antigenic peptides to alpha-2-macroglobulin; and administering to said subject at least one treatment modality that does not comprise a alpha-2-macroglobulin, wherein the at least one treatment modality comprises a chemotherapeutic agent.

Claim 3 is interpreted as a method of treating a type of cancer, comprising administering to a subject in need of such treatment a composition comprising a population of complexes, said complexes comprising (a) alpha-2-macroglobulin, and (b) antigenic proteins, wherein said population of complexes were produced by a method comprising (a) exposing a protein preparation comprising at least 50 different proteins present in cells of said type of cancer to ATP, guanidium hydrochloride, and/or acidic conditions, to produce a population of antigenic peptides; (b) recovering the population of antigenic peptides; and (c) complexing the population of antigenic peptides to alpha-2-macroglobulin; and administering to said subject at least one treatment modality that does not comprise a alpha-2-macroglobulin, wherein the at least one treatment modality comprises a chemotherapeutic agent.

Claims are further limited wherein said population of complexes comprising alpha-2-macroglobulin, and antigenic proteins is purified, the cells of said type of cancer are from a metastasis, the cancer treated is a metastasis, said composition is administered before, concurrently with, or after administration of the at least one treatment modality comprising a chemotherapeutic agent, the subject has previously been non-responsive to treatment with said at least one treatment modality comprising a chemotherapeutic agent in the absence of said composition, said administering of said composition is repeated at weekly intervals, said administering of said composition is repeated at the same site of the subject, said administering of said composition is intradermally or subcutaneously, wherein a sub-optimal amount of said composition is administered, a sub-optimal amount of said at least one treatment modality comprising

a chemotherapeutic agent is administered, the subject is human, and the antigenic protein are autologous to the subject.

Li teaches a method of treating cancer in a subject, and a method for improving the treatment outcome in a subject in need of treatment for cancer comprising (a) administering to the subject a sub-optimal amount of a purified alpha-2-macroglobulin preparation comprising a population of non-covalent alpha-2-maroglobulin-pepide complexes obtained from cancerous tissue of the subject; and (b) administering to the subject at least one treatment mortality, wherein the alpha-2-marcoglobulin preparation can be administered concurrently, before, or after the administration of the treatment modality, wherein the treatment modality include chemotherapeutic agents (see column 6, lines 16-40) and the subject is a human (see column 13, line 46). Li teaches that that antigenic peptides and/or components can be eluted from HSP/α2M complexes either in the presence of ATP or low pH, and once isolated, they can be purified and complexed in vitro to HSP or α2M to form the HSP or α2M complexes of the invention (see column 42, lines 46-67, and column 43). Li teaches that the α2M complexes can also be prepared by mixing α2M-polypeptide and antigenic molecules in the presence of a protease (see column 48, lines 33-67). Li teaches that such α2M-peptide complexes are preferably autologous to the individual subject, i.e., obtained from the tissues of the subject receiving the administration of α2M-peptide preparation and treatment modality (see column 8, lines 18-23), and the autologous α2M-peptide complexes can be isolated from a metastasis tumor (see column 12, lines 18-21). Li teaches that the α2M preparation and the therapeutic modality are administered in a sub-optimal amount (see

column 29, lines 13-15, and column 52, lines 41-54). Li teaches treating tumors that are non-responsive to chemotherapy/cytokine treatment (see column 31, lines 38-42). Li teaches intradermal and subcutaneous administration of α2M-peptide preparation (see column 51, lines 12-21). Li teaches that the α2M-peptide complexes can be administered weekly for about 4-6 weeks (see column 50, lines 46-49) and the preparation can be administered to the same or different sites (see column 30, lines 9-10). Li et al. teaches that α2M preparation may include crude cell lysate comprising α2M , and the amount of lysate corresponding to between 100-10^8 cell equivalents (see column 12, lines 24-27). Such α2M preparation would comprise at least 50 different proteins. Thus, Li teaches all the limitations of the claims.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armen (WO 02/11669A2, 2/14/2002) in view of the teachings of Srivastava (US Patent No. 6,168,793, Data of Patent 1/2/2001).

The interpretation of the claims are set forth above (see paragraph 11).

Armen teaches a method of treating a primary and metastatic cancer in a subject comprising administering a composition to said subject, wherein the composition

comprises an α2M, a saponin and an antigenic molecule, the antigenic molecule displays the antigenicity of an antigen of a cancerous cell, the antigenic molecule can be covalently or noncovalently bound to the α2M (see abstract, and page 14, lines 7-8), and the subject is a human (see page 74, line 21). Armen teaches the composition of the invention can comprise three antigenic molecules (see page 13, lines 10-14). Armen teaches that the composition of the invention can be administered alone or in combination with one or more chemotherapeutic agents, wherein the chemotherapeutic agent is administered prior or subsequent to administration of composition comprising α2M preparation (see page 73, lines 16-34). Armen teaches that the α2M, and/or antigenic molecules are preferably autologous to the individual, and can be isolated as naturally-occurring complexes from cancer cells or can be chemically synthesized or recombinantly produced (see page 15, lines 3-7). Armen teaches that the α2M/antigenic peptide complexes can be prepared in the presence of a proteinase (see page 22, lines 34-36 and page 23). Armen teaches that the antigenic peptides can be isolated by using ATP or low pH reagents such as trifluoroacetic acid (TFA) (see page 31). Armen teaches that the composition of the invention can be administered intradermally or subcutaneously once weekly for about 4-6 weeks (see page 68, line 30), wherein the same site can be repeated after a gap of one or more injections (see page 74, lines 1-12). Armen teaches that the immunogenic composition of the invention comprises sub-immunogenic amounts of its individual components (see page 75, lines 1-9). Because the instant claims use the word "comprising" which is open language, the

composition recited in the instant claims does not exclude other agents such as saponin used in Armen's composition.

Armen does not teach the composition comprises a population of complexes of α2M and antigenic proteins. However, these deficiencies are made up for in the teachings of Srivastava.

Srivastava teaches a method of treating a mammal having a tumor comprising administering a therapeutically effective amount of a purified population of non-covalent heat shock protein 70-peptide complexes to a first mammal having a tumor, wherein said population comprises a plurality of different non-covalent heat shock protein 70-peptide complexes, each of said different complexes containing a different peptide, and wherein said population of non-covalent heat shock protein 70-peptide complexes is isolated from tumor tissue of the same type as said tumor of a second mammal, wherein the first mammal and send mammal are the same (see claims 39-41). Srivastava teaches the immunogenic composition of the invention are ideal vaccination because the hsp 70-peptide complex has a number of different peptides associated with it, which potentially may include a number of different antigens capable of binding to a variety of epitopes and are capable of binding the entire spectrum of antigenic peptides regardless of the MHC haplotype of a given cells (see column 5, lines 25-50). Because the Hsp70-peptide complexes of Srivastava are isolated from a tumor cell lysate (see example 5), thus such complexes include a mixture of all Hsp70-peptides that may be presented in the tumor cell. Therefore, the complexes of Srivastava would comprise at least 50 different proteins.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Armen to use a composition comprising a population of α2M complexes to treat a metastatic cancer in view of the teachings of Srivastava. One would have been motivated to modify the method of Armen to use a composition comprising a population of α2M complexes to treat a metastatic cancer because Srivastava teaches the complexes that comprise a population of α2M complexes are capable of binding the entire spectrum of antigenic peptides in a tumor cell, and as such they would be more effective than a composition of which comprises only one or three α2M complexes. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to modify the method of Armen to use a composition comprising a population of α2M complexes to treat a metastatic cancer because Srivastava teaches a method of making a composition comprising a population of hsp70-peptide complex and is successful on treating cancer using such composition, Armen teaches a method of treating cancer using a complex comprising three hsp-peptide complexes or three α2M-peptide complexes, and moreover, Armen demonstrates that α2M works in a way that is very similar to heat shock proteins by presenting the tumor antigenic peptides to the immune cells.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-50 of U.S. Patent No. 6,984,389, in view of the teachings of Armen (WO 02/11669A2, 2/14/2002).

The interpretation of claims 1-3, 15, 17, 19, 20, 23, 25-33 and 35 has been set forth above (see paragraph 11).

Claims 48-50 of US Patent No.6,984,389 are drawn to a method for treating cancer in a subject, a method for improving the treatment outcome in a subject in need of treatment for cancer comprising the steps of:

(a) administering to said subject a sub-optimal amount of a purified alpha-2-macroglobulin preparation comprising a population of alpha-2-macroglobulin-peptide complexes that (i) display the antigenicity of a tumor-specific antigen or tumor-associated antigen of said type of cancer or (ii) are isolated from cancerous tissue of said subject; and

(b) subsequenct to step (a), administering to said subject at least one treatment modality in an amount effective for treatment of said cancer; wherein said at least one treatment modality comprises a tyrosine kinase inhibitor; wherein in the absence of step (b), said sub-optimal amount is ineffective for treatment of said cancer and wherein in the absence of step (a), said cancer does not respond to said treatment modalities. Because the population of α2M complexes is isolated from cancerous tissue of said subject, such population of α2M complexes would include a mixture of all α2M complexes presented in cancerous cells, thus would comprises at least 50 different proteins.

Claims 48-50 of US Patent No.6,984,389 do not teach that the population of complexes is produced by exposing the protein preparation comprising at least 50 different proteins to protease, ATP and/or acidic conditions. Claims 48-50 of US Patent No.6,984,389 do not teach intradermal or subcutaneously administration of the composition to the same site of the subject at weekly intervals. However, these deficiencies are made up for in the teachings of Armen.

Armen teaches that the α2M/antigenic peptide complexes can be prepared in the presence of a proteinase (see page 22, lines 34-36 and page 23). Armen teaches that the antigenic peptides can be isolated by using ATP or low pH reagents such as trifluoroacetic acid (TFA) (see page 31). Armen teaches that the composition of the invention can be administered intradermally or subcutaneously once weekly for about 4-6 weeks (see page 68, line 30), wherein the same site can be repeated after a gap of one or more injections (see page 74, lines 1-12).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one would have been motivated to prepare the composition recited in claims 48-50 of US Patent No.6,984,389 by exposing the protein preparation to a proteinase, ATP or a low pH reagent and administer the composition intradermally or subcutaneously to the same site of the subject once weekly to treat cancer in view of the teachings of Armen because the method of preparing α2M/antigenic peptide in the presence of a protease, ATP or low pH reagents is well known in the art as shown by the teachings of Armen. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to prepare the composition recited in claims 48-50 of US Patent No.6,984,389 by exposing the protein preparation to a proteinase, ATP or a low pH reagent and administer the composition intradermally or subcutaneously to the same site of the subject once weekly to treat cancer because such methods are well known in the art as taught by Armen.

Because the tyrosine kinase inhibitor is one type of at least one treatment modality, the teachings of claims 48-50 of US Patent No. 6,984,389 anticipate this specific limitation i.e. at least one treatment modality.

Claim 1-3, 15, 17, 19, 20, 23, 25-33 and 35 are directed to an invention not patentably distinct from claims 48-50 of commonly assigned US Patent No. 6,984,389 for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent No. 6,984,389, discussed above, would

form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

16. Claims 1-3, 19, 20, 23, 25, 32, 33 and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-4 and 8 of copending Application No. 10/546,106 in view of in view of the teachings of Armen (WO 02/11669A2, 2/14/2002).

This is a provisional obviousness-type double patenting rejection.

The interpretation of claims 1-3, 19, 20, 23, 25, 32, 33 and 35 is set forth above (see paragraph 11).

Claims 2-4 and 8 of copending Application No. 10/546,106 are drawn to a method for treating a cancer in a patient comprising the steps of a) isolating a complex of α2M from a bodily fluid of a mammal having said cancer; and b) administering an

amount of said isolated complex effective to treat said cancer in said patient, wherein the complex is a population of complexes of α2M bound to different antigenic molecules in which the different antigenic molecules comprise on which has the antigenicity of an antigen specific to said cancer, the antigenic molecule is derived from a tumor, the method further comprising, prior to or at the same time as step b), the step of administering a chemotherapeutic agent to said patient. Because the complex of α2M is isolated from a bodily fluid and is a population of complexes of α2M, such population would include all the mixtures of α2M complexes presented in a bodily fluid, thus would comprise at least 50 different proteins.

Claims 2-4 and 8 of copending Application No. 10/546,106 do not teach that the population of complexes are produced by exposing the protein preparation comprising at least 50 different proteins to protease, ATP and/or acidic conditions, and complexing the population of antigenic peptides to α2M. However, these deficiencies are made up for in the teachings of Armen.

Armen teaches that the α2M/antigenic peptide complexes can be isolated as naturally-occurring complexes from cancer cells or can be chemically synthesized or recombinantly produced (see page 15, lines 3-7). Armen teaches that the α2M/antigenic peptide complexes can be prepared in the presence of a proteinase (see page 22, lines 34-36 and page 23). Armen teaches that the antigenic peptides can be isolated by using ATP or low pH reagents such as trifluoroacetic acid (TFA) (see page 31), then complexed to α2M.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one would have been motivated to modify the method of claims 2-4 and 8 of copending Application No. 10/546,106 to prepare the α2M complexes in the presence of a proteinase, ATP or a low pH reagent because Armen teaches that α2M complexes can be isolated as naturally-occurring complexes from cancer cells or can be chemically synthesized or recombinantly produced (see page 15, lines 3-7) and the method of preparing α2M/antigenic peptide in the presence of a protease, ATP or low pH reagents is well known in the art as shown by the teachings of Armen. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to prepare the composition recited in claims 2-4 and 8 of copending Application No. 10/546,106 in the presence of a proteinase, ATP or a low pH reagent because such methods are well known in the art as shown by the teachings of Armen.

Claim 1-3, 19, 20, 23, 25, 32, 33 and 35 are directed to an invention not patentably distinct from claims 2-4 and 8 of commonly assigned copending Application No. 10/546,106 for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 10/546,106, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can,

under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
Aug. 2, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER